PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Roberts *et al.*

Serial No.: 10/655,547

Filed: September 4, 2003

For: COMPOSITIONS AND METHODS FOR EARLY PREGNANCY DIAGNOSIS

Group Art Unit: 1641

Examiner: Changhwa J. Cheu

Atty. Dkt. No.: UVMO:003USC1

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REPLY BRIEF

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REPLY BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellants hereby submit an original and two copies of this Reply Brief in response to the Examiner's Answer. The due date for this Reply Brief is January 27, 2006 in view of the mailing of the Examiner's Answer on November 27, 2006.

No fees are believed due in connection with this paper. However, should any other fees be due, or the attached fee is deficient or absent, the Commissioner is authorized to withdraw the appropriate fee from Fulbright & Jaworski L.L.P. Deposit Account No. 50-1212/UVMO:003USC1.

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I. REAL PARTY IN INTEREST

The Real Party in Interest is the assignee, The Curators of the University of Missouri.

II. RELATED APPEALS AND INTERFERENCES

There are no appeals or interferences for related cases.

III. STATUS OF THE CLAIMS

Original claims 1-181 were canceled and claims 182-196 added via a preliminary amendment during prosecution. Claims 182-196 are currently pending and have been finally rejected. A copy of the appealed claims is provided in the Claims Appendix.

IV. STATUS OF AMENDMENTS

No amendments were made subsequent to the Final Office Action.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention relates to methods for detecting pregnancy comprising detection of pregnancy associated antigens (PAGs). Specification from page 5, line 1 to page 7, line 3. The PAGs are present early in pregnancy and undetectable at about two months post-partum. Specification at page 4, line 20, to page 5, line 6.

VI. GROUND OF REJECTION TO BE REVIEWED ON APPEAL

As the Examiner has withdrawn the rejection under 35 U.S.C. § 112, first paragraph, regarding enablement of claims 182-196, only one ground of rejection to be reviewed on appeal remains: Were claims 182-196 properly rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement?

VII. REPLY

As noted above, the Examiner has withdrawn the previously made enablement rejection and therefore the only issue now on appeal is the written description rejection of claims 182-196 under 35 U.S.C. § 112, first paragraph. The Examiner's Answer fails to set forth a basis for maintaining this rejection for the , as set forth below.

A. The Written Description Requirement Has Been Improperly Applied

The Examiner's Answer ("Answer") continues to assert that the specification fails to satisfy the written description requirement. In particular, the Answer focuses on two cases in which the Federal Circuit addressed the applicability of the written description requirement to DNA-related inventions: *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997) and *Enzo Biochem. Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 63 U.S.P.Q.2d 1609 (Fed. Cir. 2002). Citing to these cases for support, the Examiner concludes the following:

> In this case, the specification does not describe all the PAGs required to practice the method of claim 182 in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any PAG, nor does the specification provide any physical or chemical characteristics of the other PAGs nor any *functional characteristics coupled with a known or disclosed correlation between structure and function* (emphasis added).

Answer at p. 5 (emphasis in original). Applicants respectfully traverse.

The Examiner's arguments improperly blend the ***separate*** standards that permit satisfaction of the written description requirement. The Written Description Guidelines ("Guidelines") as recited in MPEP § 2163, which cite *Lilly* and *Enzo* in large part, state the following:

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by

(1) actual reduction to practice,

(2) reduction to drawings, ***or*** by

(3) disclosure of relevant, identifying characteristics, *i.e.*,

(a) structure or other physical and/or chemical properties,

(b) by functional characteristics coupled with a known or disclosed correlation between function and structure, ***or***

(c) by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus."

Id. (emphases and indenting added). This is consistent with the Federal Circuit case law, which makes clear that written description need not be satisfied in any one particular way and noting that an applicant may describe the claimed subject matter by "whatever characteristics sufficiently distinguish it." *Amgen v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206 (Fed. Cir. 1991). Thus, there are at least the three separate means identified in the Guidelines by which a disclosure may satisfy the written description requirement regarding a claimed genus, the third of which entails three further, ***separate*** options. That is, if a disclosure meets either of (a), (b) or a combination thereof according to (c) sufficient to show possession of a claimed genus, the written description requirement has been satisfied. More specifically concerning element (b), a showing of correlation between structure and function is only one means by which an applicant may satisfy the written description requirement.

Yet the Examiner improperly reads into the written description requirement such a showing, separating the requirements of (a), (b) and (c) and imparting the "correlation" requirement of (b) into the separate requirement of (a) and arguably (c) as well. Indeed, nearly every aspect of the Answer and all of the rejections to date rest on this improper interpretation of the Guidelines, *Lilly* and *Enzo*. A showing of correlation is ***not*** required by the Guidelines as a

means of satisfying the written description requirement. It is this improper blending of the separate means by which the written description requirement may be satisfied that cannot support a written description rejection.

For example, in the section of the Answer named "(9) Grounds of Rejection," the Examiner blends the *Lilly* requirement, pertaining to "structural features common to the members of the genus, which features constitute a substantial portion of the genus," with the following statement, "However, there is no further study correlating [a region of 'some sequence identity'] to the asserted function…" The Action, pp 5-6. This is not a requirement of the *Lilly* holding or the Guidelines and this statement is just the first of several instances in which the "correlation" standard is improperly combined with other, separate standards for satisfying the written description requirement.

In the section entitled, "(10) Response to Argument," the Examiner attempts to counter Appellants' showing that the specification provides a sufficient structural description of representative PAGs by stating:

> *"[I]t* is not mainly *the number, i.e. how many PAGs, is disclosed in the specification. It rests also in the correlation of structure and functionality. Examiner pointed out that the specification does not provide sufficient analysis or data establishing or corroborating such correlation, therefore the specification fails to support the full scope of claims."*

Answer at p 6. Here, the Examiner demands that the correlation requirement be met and because it allegedly has not, the Examiner maintains the written description rejection. This is further reflected at p 7 of the Answer, wherein it is stated that it is not merely the seven PAGs disclosed that fail to provide written description for the full claim scope, "but ***also*** want of correlation with respect to the functionality." (emphasis added). Again, holding Appellants to such a standard is legally erroneous.

This improper analysis is echoed in the next section of the Response to Argument, wherein the Examiner asserts that "the conserved regions among diversity [of PAGs] [do] not amount to justification of possessing the whole genus ***without further correlation study***." Answer, p 7. The Examiner continues: "Rather the main concern is whether these seven PAGs are sufficient to provide information with respect to the ***correlation*** of functionality and structure to one [of] ordinary skill in the art." Answer, p 8 (emphasis in original). The Examiner therefore appears to indicate that it is not enough that the seven PAGs shown share a structure and function, but rather it must be shown ***why*** they do, *e.g.*, which specific amino acids are responsible for the function. This is incorrect and expressly contrary to Federal Circuit case law holding that "it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *See Newman v. Quigg*, 877 F.2d 1575, 1581, 11 U.S.P.Q.2d 1340, 1345 (Fed. Cir. 1989).

In sum, all of the Examiner's arguments are improperly based on the legally faulty premise that Applicants' must show a correlation between structure and function to satisfy the written description requirement, and that this showing must amount to an identification of the specific sequences conferring the recited function. The rejection should therefore be reversed on this basis alone, even putting aside the fact that Applicants specification does demonstrate that a correlation exists between the structure of the PAGs recited in the claims and their function, as set forth below.

B. A Correlation Exists Between Structure and Function Regarding the PAGs Recited in the Claimed Invention

While it has been established above that Appellants are not required to set forth a correlation between structure and function in order to satisfy the written description requirement, such a correlation nonetheless exists with respect to the claimed invention. Contrary to the Examiner's assertions, the specification includes working examples and figures, describing just such a correlation of structure (disclosed sequences and sequence comparisons) and functionality (presence of PAGs early in pregnancy and undetectability two months post-partum) that allow one of skill in the art to identify PAGs in compliance with § 112, first paragraph.

The structures of PAGs encompassed by the present claims have been clearly set forth in the disclosure. For example, the specification provides in the sequence listing the amino acid and nucleic acid sequences for BoPAGs 4, 6, 7, 16, 17, 20 and 21, which the Examiner acknowledges share the function of being present early in pregnancy and undetectable at about two months post-partum. *See, e.g.,* Specification, p 10, line 10, to p 13, line 2; Final Action, p 10. While there is some degree of structural diversity among PAGs and some PAGs sharing sequence identity are not present early in pregnancy and undetectable two-months post-partum, there is also structural conservation among those that do. Those sequences not meeting the claimed criteria are readily identified using the assays described in the working examples, and in any event are excluded from the scope of the claims. With respect to sequence, FIG. 4, for example, shows ***substantial identity*** among bovine PAGs at both the nucleic acid and amino acid level. This conservation is further illustrated in the sequence alignments provided in FIG. 1 and the phylogenic tree provided in FIG. 5. The alignments show both conserved regions and indicate a common ancestry. All of this evidence points to a sufficient disclosure of shared structural characteristics of PAGs.

Regarding function, the disclosed PAGs are naturally occurring proteins in the bovine placenta; their "function" for the purpose of the claimed invention is not what internal purpose they serve in a bovine animal, but rather the "function" of being present early in pregnancy and undetectable at about two months post-partum, thereby allowing pregnancy detection according to the claimed methods. Indeed the specification provides data on the timing of PAG expression and presence in placental tissue (*e.g.*, Examples 3-4 at pp 62-67). The functional aspect of the present claims, as supported by the specification, is therefore captured by the claim language "[wherein the PAG] is present early in pregnancy and is undetectable at about two months post-partum." Applicants are thus claiming no more than what was invented.

The correlation between the structural and functional aspects described above lies in the fact that, in addition to description of seven representative PAGs acknowledged by the Examiner, all of the assays and methodology for identifying and confirming PAGs meeting the claimed criteria are described in the specification and working examples. This includes analysis of sequences (as characterized in the specification, such as FIGs 1, 4 and 5), function (via, for example, assays as described at pp 50-58 and Example 3) and the fact that the genus of sequences is finite and limited by what PAGs are produced in a bovine animal. That is, the biology of the animal dictates a finite and limited class of PAGs, narrowly defining the genus and illustrating that the species acknowledged by the Examiner are representative. In view of this the specification provides more than an adequate written description for the claims in accordance with the written description requirement.

C. The Examiner's Arguments Regarding Site-Directed Mutagenesis are Inapposite

The Examiner appears to suggest that site-directed mutagenesis provides the ***only way*** a structure-function correlation can be established in the present case. For example, it is stated that "there is no further study correlating [the regions of common sequence identity among PAGs] to

the asserted function... using site-directed mutagenesis. Thus, the specification does not provide an adequate written [description]...." Answer, p 6. However, nothing in the Guidelines or case law sets forth or suggests the requirement that a structure-function correlation must be shown via site-directed mutagenesis. Furthermore, Appellants are ***not*** required to show how or why the claimed invention works. *See Newman v. Quigg*, 877 F.2d 1575, 1581, 11 U.S.P.Q.2d 1340, 1345 (Fed. Cir. 1989).

The PAGs recited in the claims are not defined, for instance, by a shared enzymatic activity that might be studied via, *e.g.*, site-directed mutagenesis. Such a technique would presumably require genetically altering the genome of bovine animals to express various mutagenized PAG sequences, impregnating the animals and then analyzing the expression of the mutant PAGs. This would make no sense scientifically or with regard to the legal requirements of §112. The point of the pregnancy detections methods disclosed in the application is to determine if an animal is pregnant, not to find out ***why*** a molecule has an expression profile suitable for so determining by mutating it and reintroducing it back into a transgenic animal. As indicated previously, PAGs are expressed endogenously and therefore finite in number. If one of skill in the art wants to determine whether a specific PAG is present early in pregnancy and undetectable about two-months post-partum, that individual only needs to follow the very working examples in the specification providing assays for confirming this. Site-directed mutagenesis would not achieve this and at best might serve some whimsical scientific curiosity. The Examiner's contentions in this regard are therefore irrelevant and further illustrate the legal error upon which the rejection is based.

D. The Specification Satisfies the *Lilly* Standard

As noted in the Answer, the disclosure may satisfy the written description requirement regarding a genus/species claim under *Lilly* by:

> **structurally describing a representative number of PAGs that are capable of being an early pregnancy detector of bovine and become undetectable about 2 months post-partum, or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus."**

Answer, page 5 (emphasis added). *See also* MPEP § 2163. The Examiner asserts that the present disclosure fails to satisfy either of these aspects. Applicants respectfully disagree.

To support the assertion that the disclosure fails to satisfy the first aspect, "structurally describing a representative number of PAGs…", the Examiner states that the "diversity" of amino acid and nucleic acid compositions of boPAG2 through boPAG12 would not permit a person of skill in the art to conclude that Appellants had sufficiently described a "representative number" of such species. Answer, p 5. Yet the Examiner acknowledges that the specification teaches ***seven*** PAGs that fall within the scope of the claims, and these are the subject of the issued parent case. The Examiner nonetheless repeatedly states that the specification fails to provide the complete structure of ***any*** PAG (Answer, p 5). This is wholly incorrect, as the amino acid and nucleic acid sequences for the aforementioned seven PAGs (boPAGs 4, 6, 7, 16, 17, 20 and 21) are provided in the specification. *See e.g.,* Specification, p 10, line 10, to p 13, line 2.

Further, Appellants respectfully again note that if the Examiner has a basis for asserting that these seven described PAGs do not constitute a representative number of species within the genus of bovine PAGs that are present early in pregnancy and are undetectable at about two months post-partum, then the Examiner should be able to explain what number would be representative. No such basis or number has been provided. The Examiner's vague reference to

"structural diversities" among different PAGs (Answer, p 5) fails to substantiate a rejection on the grounds that the present specification does not disclose "a representative number" of species under the *Lilly* standard. Appellants respectfully submit that the *Lilly* standard has been satisfied in this regard at least by the ***seven*** acknowledged PAGs alone.

The Examiner also asserts that the specification fails to satisfy the *Lilly* requirement of setting forth "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Answer, p 5; *see* MPEP § 2163 and *Lilly*, 119 F.3d at 1568, 43 U.S.P.Q.2d at 1406. While the Examiner concedes that "some sequence identity" has been disclosed, it is stated that "there is no further study correlating this region to the asserted function." Answer, p 6. Again, this is not a requirement of *Lilly*, *Enzo* or the Guidelines. These authorities are clear that a correlation is only one way of satisfying written description. *See* MPEP § 2163; *Lilly*, 119 F.3d at 1568, 43 U.S.P.Q.2d at 1406. The present specification more than adequately describes the full scope of claimed invention by way of representative sequences, as well as by way of demonstrating a structure-function correlation, coupled with teaching describing the methodology for identifying and confirming PAGs in accordance with the claims.

Reversal of the rejection is thus respectfully requested.

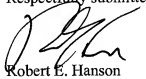
E. The Rejections Under 35 U.S.C. § 112, First Paragraph Are Now Moot

The Examiner's Answer withdraws the previously made rejections of claims 182-196 under 35 U.S.C. § 112, first paragraph, for an alleged lack of and enablement. The appeal of this rejection is therefore now moot.

CONCLUSION

It is respectfully submitted, in light of the above, that none of the pending claims are properly rejected. Reversal of the pending grounds for rejection is thus respectfully requested.

Respectfully submitted,



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Date: January 29, 2007

VIII. CLAIMS APPENDIX

182. A method for detecting pregnancy in a bovine animal comprising:
   (a) obtaining a sample from said animal; and
   (b) detecting at least one pregnancy associated antigen (PAG) in the sample that is present early in pregnancy and is undetectable at about two months post-partum; whereby detection of the PAG indicates that the animal is pregnant.

183. The method of claim 182, wherein said sample is selected from the group consisting of saliva, serum, blood, milk or urine.

184. The method of claim 182, wherein said detecting comprises ELISA.

185. The method of claim 182, wherein said detecting comprises RIA.

186. The method of claim 182, wherein said detecting comprises Western blot.

187. The method of claim 182, wherein detecting is carried out by immunologic detection.

188. The method of claim 187, wherein immunologic detection comprises detection with polyclonal antisera.

189. The method of claim 187, wherein immunologic detection comprises detection with a monoclonal antibody preparation.

190. The method of claim 182, wherein detecting comprises RNA detection.

191. The method of claim 182, further comprising detecting at least two PAGs in said sample.

192. The method of claim 191, further comprising detecting at least three PAGs in said sample.

193. The method of claim 184, wherein said ELISA is a sandwich ELISA comprising binding the PAG to a first antibody preparation fixed to a substrate and a second antibody preparation labeled with an enzyme.

194. The method of claim 193, wherein said enzyme is alkaline phosphatase or horseradish peroxidase.

195. The method of claim 193, wherein said first antibody preparation is monoclonal.

196. The method of claim 193, wherein said first antibody preparation is polyclonal.

IX. EVIDENCE APPENDIX

No exhibits.

X. RELATED PROCEEDINGS APPENDIX

There are no related proceedings.